The amendment to claim 13 are supported by the specification at, for instance, page 13, lines 14-25. Claim 13 is also amended to clarify the scope of the claim.

The amendment to claim 14 is supported by, for instance, originally filed claim 20 and by the specification at, for instance, page 13, lines 18-25.

The amendment to claims 21, 22, 26, and 29-30 is supported by the specification at, for instance, page 8, lines 1-5, and page 22, lines 7-11.

The amendment to claim 35 is supported by the specification at, for instance, page 3, line 29 through page 4, line 1.

New claim 37 is supported by the specification at page 13, lines 22-25.

New claim 38 is supported by, for instance, originally filed claim 1 and the specification at page 13, lines 15-17 and lines 22-25.

New claim 39 is supported by, for instance, originally filed claim 14 and the specification at page 13, lines 15-17 and lines 22-25.

New claim 40 is supported by, for instance, originally filed claim 13 and the specification at page 13, lines 14-15 and lines 22-25.

New claim 41 is supported by, for instance, originally filed claim 27 and the specification at page 8, line 25 through page 9, line 4.

New claim 42 is supported by, for instance, originally filed claim 28 and the specification at page 8, line 25 through page 9, line 4.

New claim 43 is supported by, for instance, originally filed claim 4 and the specification at page 13, lines 14-25.

New claims 44, 46 and 48 are supported by the specification at page 13, lines 22-25.

New claim 45 is supported by, for instance, originally filed claim 10 and the specification at page 13, lines 14-25.

New claim 47 is supported by, for instance, originally filed claim 18 and the specification at page 13, lines 14-25.

New claim 49 is supported by the specification at, for instance, page 14, lines 18-19, and page 21, lines 4-6.

New claim 50 is supported by the specification at, for instance, page 21, lines 14-16.

New claim 51 is supported by the specification at, for instance, page 21, lines 2-3.

Information Disclosure Statement

An Information Disclosure Statement was mailed 7 December 1999; however, it does not appear that the documents cited therein were considered by the Examiner. The Examiner is requested to return a copy of the 1449 form, marked as being considered and initialed by the Examiner, with the next Official Communication. A copy of the 1449 is enclosed for the Examiner's convenience.

Rejection Under 35 U.S.C. § 112, First Paragraph

The Examiner rejected claims 4, 10, 13, and 18 under 35 U.S.C. § 112, first paragraph, because the specification, while being enabling for detecting whether an individual is at risk for developing spinocerebellar ataxia type 8, does not reasonably provide enablement for determining whether or not an individual has SCA8. Specifically, it was asserted that the specification lacks guidance to enable one skilled in the art to diagnose ataxia type 8 based on the presence of CTG repeat expansions. This rejection is respectfully traversed.

The specification states that the term "diagnosis" can be the presymptomatic identification of individuals at-risk for ataxia, including the identification of individuals where there is no family history of the disease (specification, page 10, line 30 through page 11, line 1). "At-risk" is defined as an individual having an allele of the SCA8 coding sequence that is associated with spinocerebellar ataxia type 8 (specification, page 8, lines 6-7). This includes an individual who may be manifesting at least one symptom of spinocerebellar ataxia, as well as an individual who may develop at least one symptom of spinocerebellar ataxia in the future (specification, page 8, lines 7-10). Diagnosis can also mean the identification, in an individual displaying at least one symptom of ataxia, of the genetic basis of the at least one symptom (specification, page 11, lines 1-3). It is disclosed that the symptoms of spinocerebellar ataxia type 8 include mild aspiration and gait instability, spastic and ataxic dysarthria, nystagmus, limb

and gait ataxia, limb spasticity and diminished vibration perception (specification, page 7, lines 28-30). Severely affected individuals can become non-ambulatory (specification, page 7, lines 30-31).

It is disclosed that the mapping and cloning of the SCA8 coding sequence allows the definitive diagnosis of one type of the dominantly inherited ataxias using a simple test of a biological specimen, for instance blood (specification, page 21, lines 21-23). The diagnostic methods of the present invention can involve known methods for detecting a specific DNA fragment, including direct detection of the DNA or indirect detection through the detection of RNA, for example (specification, page 14, lines 13-15). Typically the number of CTG repeats present in the repeat region of an SCA8 allele can be determined (specification, page 13, lines 13-14). Generally, an at-risk allele of SCA8 is an allele with at least about 80 CTG repeats in an SCA8 repeat region (specification, page 13, lines 14-15). Generally, an SCA8 allele with less than 80 CTG repeats is a normal allele, which is indicative of an individual who will not develop symptoms of spinocerebellar ataxia type 8 (specification, page 13, lines 15-17). Preferably, the number of CTG and CTA repeats present in the repeat region of an SCA8 allele can be determined (specification, page 13, lines 18-19). An at-risk allele is preferably one with at least about 92 combined CTA and CTG repeats in a repeat region of an SCA8 coding sequence (specification, page 13, lines 19-21). An SCA8 allele having no greater than about 91 combined CTA and CTG repeats in a repeat region of an SCA8 coding sequence, preferably no greater than about 33, generally indicates an allele of the SCA8 coding sequence that is normal (page 13, lines 22-25).

In the interests of furthering prosecution, claims 4, 10, and 18 have been amended to recite "wherein an individual who has or is at risk for developing SCA8 has an at-risk allele having at least about 80 CTG repeats in the repeat region or at least about 92 combined CTA and CTG repeats in the repeat region." Regarding claim 13, the Examiner is requested to note that claim 13 recites "wherein individuals who are <u>not</u> at-risk for developing spinocerebellar ataxia type 8 have less than 80 CTG repeats in the repeat region or no greater than about 91 combined CTA and CTG repeats in the repeat region" (emphasis added). The preamble of claim 13 has

been amended to clarify the scope of the claim.

The Examiner is respectfully requested to reconsider and withdraw the rejection of claims 4, 10, 13, and 18 under 37 C.F.R. §112, first paragraph.

Rejection Under 35 U.S.C. § 112, Second Paragraph

The Examiner rejected claims 1-20, 33, and 34 under 35 U.S.C. § 112, second paragraph. This rejection is respectfully traversed.

According to the Action at page 4, "[t]he claims recite the phrase 'complementary oligonucleotides' which is indefinite." The Examiner is respectfully requested to note that the claims do not recite the phrase "complementary oligonucleotides." It is Applicants' position that the term "complementary" is well known to a person of skill in the art, and that such a person would recognize the metes and bounds of the subject matter of the claims that recite the term "complementary," particularly in view of the disclosure. The specification states that the term "complement" and "complementary" as used herein, refers to the ability of two DNA molecules to base pair with each other, where an adenine on one DNA molecule will base pair to a guanine on a second DNA molecule and a cytosine on one DNA molecule will base pair to a thymine on a second DNA molecule (specification, page 9, lines 23-27). Two DNA molecules are complementary to each other when a nucleotide sequence in one DNA molecule can base pair with a nucleotide sequence in a second DNA molecule (specification, page 9, lines 27-29). For instance, the two DNA molecules 5'-ATGC and 5'-GCAT are complementary, and the complement of the DNA molecule 5'-ATGC is 5'-GCAT (specification, page 9, lines 29-31). The term complement and complementary also encompasses two DNA molecules where one DNA molecule contains at least one nucleotide that will not base pair to at least one nucleotide present on a second DNA molecule (specification, page 9, line 31 through page 10, line 2).

Claims 1-20 were asserted to be indefinite because the claims fail to include a positive process step relating back to the preamble. Claim 1 has been amended to recite "analyzing the amplified DNA fragment for an at-risk allele having at least about 80 CTG repeats in the repeat region or at least about 92 combined CTA and CTG repeats in the repeat region." Claim 14 has

been amended to recite "analyzing the amplified DNA fragment for an at-risk allele having at least about 80 CTG repeats in the repeat region or at least about 92 combined CTA and CTG repeats in the repeat region."

Claim 7 as originally filed recites "a method for detecting the presence of at least one DNA molecule containing a repeat region of an SCA8 coding sequence comprising, inter alia, analyzing the DNA molecule for a repeat region characteristic of a normal or at-risk form of the SCA8 coding sequence." It is Applicants' position that claim 7 recites a positive process step relating back to the preamble.

Pending claim 13 recites "a method for determining whether an individual is not at-risk for developing, spinocerebellar ataxia type 8, the method comprising analyzing a repeat region of a spinocerebellar ataxia type 8 coding sequence wherein individuals who are not at-risk for developing spinocerebellar ataxia type 8 have less than 80 CTG repeats in the repeat region or no greater than about 91 combined CTA and CTG repeats in the repeat region." It is Applicants' position that claim 13 recites a positive process step relating back to the preamble.

Claims 4, 10, and 18 were also asserted to be indefinite because the claims fail to include a positive process step relating back to the preamble. Claims 4, 10, and 18 are not process claims. It is Applicants' position that claims 4, 10, and 18 should not be included in this rejection; since they are not process claims they do not require a positive process step relating back to the preamble.

The Examiner is respectfully requested to reconsider and withdraw the rejection of claims 1-20, 33, and 34 under 35 U.S.C. § 112, second paragraph.

Rejection Under 35 U.S.C. § 102(b)

The Examiner rejected claims 21-32 under 35 U.S.C. § 102(b) as being anticipated by Levitan (Textbook of Human Genetics, 3rd Ed., 1988, New York, Oxford University Press). This rejection is respectfully traversed.

Levitan discloses a historical overview of staining techniques to identify chromosome banding patterns. Different types of bandings are disclosed in karyotypes. The term karyotype

is the entire chromosomal complement of a cell or species as visualized during mitosis (Lewin, Genes VI, Oxford University Press, p. 1227 (1997)) (copy enclosed). Levitan does not disclose any isolated coding sequences. In contrast, claim 21 recites an isolated SCA8 coding sequence, comprising a repeat region, wherein the SCA8 locus is located on the long arm of chromosome 13. The cited document does not specifically disclose this. Thus, claim 21 is not anticipated by the cited document.

The Examiner is respectfully requested to reconsider and withdraw the rejection of claims 21-32 under 35 U.S.C. § 102(b) as being anticipated by the cited document.

Rejection Under 35 U.S.C. § 102(a)

The Examiner rejected claim 35 under 35 U.S.C. § 102(a) as being anticipated by Accession No. AL008632 (S. Mistry). Specifically, it was asserted that Accession No. AL008632 discloses an oligonucleotide that contains 20 nucleotides exactly complementary to SE ID NO:1. This rejection is respectfully traversed.

Accession No. AL008632 discloses 75,793 bases of nucleotide sequence from human chromosome X. In contrast, claim 35 recites an isolated oligonucleotide that hybridizes to a nucleic acid molecule containing a repeat region of an isolated SCA8 coding sequence, wherein the oligonucleotide hybridizes to the SCA8 coding sequence of the long arm of chromosome 13. Accession No. AL008632 does not disclose this. Thus, Accession No. AL008632 does not anticipate claim 35.

The Examiner is respectfully requested to reconsider and withdraw the rejection of claim 35 under 35 U.S.C. § 102(a) as being anticipated by the cited art.

Conclusion

It is respectfully submitted that the application is in condition for allowance and notification to the effect is respectfully requested.

The Examiner is invited to contact Applicants' Representatives, at the below-listed telephone number, if there are any questions regarding this Response or if prosecution of this

application may be assisted thereby.

CERTIFICATE UNDER 37 C.F.R. 1.8:

The undersigned hereby certifies that this paper is being deposited in the United States Postal Service, as first class mail, in an envelope addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231, on this 23 day of May, 2000.

Ann M. Mueting

Date

AMM:LDG:dlp

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Initiation factors (IF in prokaryotes, eIF in eukaryotes) are proteins that associate with the small subunit of the ribosome specifically at the stage of initiation of protein synthesis.
Insertion sequence (IS) is a small bacterial transposon that carries only the genes needed for its own transposition.
Insertions are identified by the presence of an additional stretch of base pairs in DNA.
Integral membrane protein is a protein (noncovalently) inserted into a membrane; it retains its membranous association by means of a stretch of ~25 amino acids that are uncharged and/or hydrophobic.
Integration of viral or another DNA sequence is its insertion into a host genome as a region covalently linked on either side to the host sequences.
Interallelic complementation describes the change in the properties of a heteromultimeric protein brought about by the interaction of subunits coded by two different mutant alleles; the mixed protein may be more or less active than the protein consisting of subunits only of one or the other type.
Interbands are the relatively dispersed regions of polytene chromosomes that lie between the bands.
Intercistronic region is the distance between the termination codon of one gene and the initiation codon of the next gene.
Intermediate component(s) of a reassociation reaction are those reacting between the fast (satellite DNA) and slow (nonrepetitive DNA) components; contain moderately repetitive DNA.
Interphase is the period between mitotic cell divisions; divided into G1, S, and G2.
Intervening sequence is an intron.
Intron is a segment of DNA that is transcribed, but removed from within the transcript by splicing together the sequences (exons) on either side of it.
Inversion is a chromosomal change in which a segment has been rotated by 180° relative to the regions on either side and reinserted.
Inverted repeats comprise two copies of the same sequence of DNA repeated in opposite orientation on the same molecule. Adjacent inverted repeats constitute a palindrome.
Inverted terminal repeats are the short related or identical sequences present in reverse orientation at the ends of some transposons.
IS is an abbreviation for **insertion sequence**, a small bacterial transposon carrying only the genetic functions involved in transposition.
Isoaccepting tRNAs represent the same amino acid.
Isotype is a group of closely related immunoglobulin chains.

Karyotype is the entire chromosomal complement of a cell or species (as visualized during mitosis).
kb (kilobase) is an abbreviation for 1000 base pairs of DNA or 1000 bases of RNA.
Kinase is an enzyme that phosphorylates (adds a phosphate group) to a substrate; the substrates for **protein kinases** are amino acids in other proteins, and they are divided into those specific for tyrosine and those specific for threonine/serine.
Kinetic complexity is the complexity of a DNA component measured by the kinetics of DNA reassociation.
Kinetochore is the structural feature of the chromosome to which microtubules of the mitotic spindle attach (*see also* centromere).

Lagging strand of DNA must grow overall in the 3′–5′ direction and is synthesized discontinuously in the form of short fragments (5′–3′) that are later connected covalently.
Lampbrush chromosomes are the large meiotic chromosomes found in amphibian oocytes.
Lariat is an intermediate in RNA splicing in which a circular structure with a tail is created by a 5′–2′ bond.
Late period of phage development is the part of infection following the start of DNA replication.
Leader is the nontranslated sequence at the 5′ end of mRNA that precedes the initiation codon.
Leader sequence of a protein is a short N-terminal sequence responsible for passage into or through a membrane.
Leading strand of DNA is synthesized continuously in the 5′–3′ direction.
Leaky mutations allow some residual level of gene expression.